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VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration HFA -305
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: **PETITION FOR STAY OF AGENCY ACTION**

Dear Madam or Sir:

The undersigned submits this Petition on behalf of Zeneca Inc., under 21 C.F.R. $10.35, requesting that the Commissioner of Food and Drugs stay the effective date of any pending, tentative, or final decision to approve an ANDA tiled by Gensia Sicor Pharmaceuticals, No. 75-433, or any other applicant, for a generic version of Zeneca's product DIPRIVAN® (propofol) Injectable Emulsion with disodium edetate, but which contains no antimicrobial additive whatsoever. We submit this request pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), and the Agency's regulations, 21 C.F.R. Part 314.

WA01B/7948.1

99P-0796

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Executive Summary

Zeneca's DIPRIVAN® (propofol) Injectable Emulsion is an anesthetic product formulated in a carrier consisting in large part of a soybean oil-based emulsion, The emulsion can support microbial growth and, although the product is terminally sterilized, once opened it is subject to possible microbial growth associated with extrinsic contamination introduced through mishandling. Following reports of fevers and infections, which were determined by the Centers for Disease Control to be the result of extrinsic contamination of the product by medical personnel in the U. S., Zeneca undertook considerable research, including clinical studies, to confirm the safety and efficacy of a new formulation, containing the antimicrobial additive disodium edetate. Zeneca submitted a supplemental New Drug Application ("sNDA'") for this new formulation. The FDA provided accelerated review and approved the application, granting the new product containing an antimicrobial additive three years of exclusivity based on the studies required for approval.[1/]

On April 7, 1998, Zeneca submitted to the FDA a Citizen Petition requesting that the FDA withdraw approval of those portions of Zeneca's NDA 19-627 that provided for a formulation of DIPRIVAN that does not contain the antimicrobial additive disodium edetate, pursuant to section

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1/ Zeneca also has obtained patent protection for the current formulation of propofol injectable emulsion, containing disodium edetate as an antimicrobial additive, and the uses thereof.

505(e) of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act") and the Agency's regulations, 21 C.F.R. $314.150. Zeneca requested withdrawal on the basis that, due to the availability of the new formulation of DIPRIVAN, which contains disodium edetate, the original formulation of DIPRIVAN had a less desirable safety profile in the context of misuse by healthcare providers. 21 U.S.C. § 355(e).[2/] Based on the evidence of safety issues associated with the mishandling of the original formulation of DIPRIVAN by health care providers, set out in Zeneca's Citizen Petition, the Agency withdrew, on safety grounds, those portions of Zeneca's NDA 19-627 that provide for a formulation of DIPRIVAN that does not contain the antimicrobial additive disodium edetate, under section 505(e) the Act and the Agency's regulations, 21 C.F.R. § 314.150. See 63 Fed. Reg. 68289 (Dec. 10, 1998). With its ANDA 75-433, Gensia Sicor is seeking approval of a generic copy of the original formulation of DIPRIVAN that has been withdrawn by the FDA for reasons of safety. It cannot do so.

FDA cannot approve an ANDA by Gensia Sicor that is based on reference to a drug which has been withdrawn by FDA for safety reasons. Further, FDA cannot approve an ANDA by Gensia Sicor that attempts to refer to the only remaining form of DIPRIVAN, which contains an

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2/ Zeneca withdrew the original formulation of DIPRIVAN from the U.S. market in 1996 for comparative safety reasons in the context of misuse, and the FDA subsequently transferred the product listing to the Discontinued Products list in the Orange Book.

antimicrobial additive, since Gensia Sicor's ANDA product contains no antimicrobial additive whatsoever, and is thus not equivalent to any reference listed drug.

Because the Agency has granted Zeneca's Citizen Petition withdrawing on safety grounds its original formulation of DIPRIVAN, Gensia Sicor therefore must submit, and obtain approval from the Agency of, a Citizen Petition requesting authorization to reference a propofol drug product, DIPRIVAN, which contains the antimicrobial additive, disodium edetate. Gensia Sicor, however, intends to eliminate the antimicrobial additive from its formulation and apparently rely cm a prefilled syringe packaging/delivery system. Even if the regulations permitted such a change, which they do not, FDA is required to refuse to approve this ANDA by Gensia Sicor because the Agency's regulations mandate that any proposed generic parenteral product that contains a change in any inactive ingredient other than a preservative, buffer, or an antioxidant cannot be approved. Disodium edetate in DIPRIVAN is not a preservative, buffer, or antioxidant and, therefore, the regulations preclude an ANDA applicant such as Gensia Sicor from making any change with respect to disodium edetate. Moreover, the regulations do not permit the Agency to approve an ANDA that relies on an NDA for a product that includes a preservative, buffer, or antioxidant, but that proposes to eliminate any such ingredients from the formulation.

Gensia Sicor cannot be allowed to make such a significant change without FDA requiring Gensia Sicor to file a Citizen Petition providing the bases upon which it believes a prefilled syringe delivery system can effectively resolve the contamination problems that led FDA to withdraw on safety grounds a version of propofol without antimicrobial additive. For FDA to do so would both deprive the public of the opportunity to comment on such significant safety issues and negate the validity of FDA's previous decision to withdraw propofol without any antimicrobial additive from sale, based on safety grounds.

There are significant safety issues and market exclusivity issues presented by Gensia Sicor's ANDA requesting Agency approval of such a parenteral product with no antimicrobial additive, First, for any substance proposed to be removed from a parenteral product like propofol injectable emulsion, the applicant must establish that the removal of the additive does not alter the safety of the drug formulation. As Zeneca discovered earlier from its experience with the original formulation of DIPRIVAN, mishandling of the product by health care professionals can cause contamination and result in significant safety and efficacy problems. Second, Zeneca has been granted exclusivity for the new formulation of DIPRIVAN effective until June 11, 1999.

Consequently, Gensia Sicor's ANDA cannot be approved by FDA until Gensia Sicor conducts appropriate clinical and other scientific investigations to confirm the safety and efficacy of the

proposed product demonstrating that it can prevent microbial growth caused by misuse of the product by healthcare professionals. The Agency must require submission of comprehensive scientific and clinical studies establishing that an alternative packaging system, such as a prefilled syringe that assertedly cannot be reused, results in the generic product having a safety, therapeutic and antimicrobial efficacy profile at least equal to that of DIPRIVAN with disodium edetate. An applicant must, therefore, submit and obtain approval of an NDA, rather than an ANDA, to meet those requirements.

I. Decision Involved

The decision as to which Zeneca seeks a stay is the FDA's pending, tentative or final decision to approve Gensia Sicor's, or any other applicant 's, ANDA for a generic version of DIPRIVAN® (propofol) Injectable Emulsion, containing disodium edetate, but which contains no antimicrobial additive whatsoever and is thus a duplicate of the original formulation of DIPRIVAN, which was withdrawn by the FDA for reasons of safety pursuant to Section 505(e) of the Act.

II. Action Requested

Zeneca requests that the FDA promptly stay any pending, tentative, or final approval of the ANDA filed by Gensia Sicor, or any other applicant, for a generic version of DIPRIVAN®

(propofol) Injectable Emulsion with disodium edetate, but which contains no antimicrobial additive whatsoever. FDA's regulations do not allow approval of such an ANDA. Even if FDA believed the regulations do allow such change, the Agency would have to stay any such decision pending submission by Gensia Sicor and approval by FDA of a Citizen Petition requesting authorization to reference DIPRIVAN with the antimicrobial additive disodium edetate, even though the proposed version contains no antimicrobial additive, and pending the expiration of the three years of market exclusivity granted to DIPRIVAN and the completion by Gensia Sicor of adequate clinical and scientific studies that demonstrate the safety of its product and delivery system.

III. Statement of Grounds

A. Background

Zeneca's DIPRIVAN® (propofol) Injectable Emulsion is a sterile, nonpyrogenic emulsion containing propofol (10/0) for inducing and maintaining anesthesia and ICU sedation. Although the product is terminally sterilized before distribution, the original DIPRIVAN formulation contained no antimicrobial additive and was, therefore, susceptible, on opening, to microbial growth within the product associated with extrinsic contamination if the product was not handled properly. In this regard, shortly after the launch of the product, Zeneca and the FDA received

reports of clusters of fever and infections associated with the failure of medical personnel in a number of hospitals in the U.S. to apply appropriate aseptic techniques in handling the product.

Because of the severity of the adverse experiences associated with mishandling of propofol injectable emulsion, and because of the inability of previous efforts to eradicate such mishandling, Zeneca began work on discovering and developing anew formulation of DIPRIVAN containing an antimicrobial additive. In December 1993, Zeneca discussed its development efforts with both the FDA and the CDC. The Agency strongly encouraged Zeneca to pursue this solution to the problem of product mishandling. Zeneca found that disodium edetate appeared to provide the desired antimicrobial effect without jeopardizing stability or creating other formulation-related safety and efficacy concerns. On December 22, 1995, Zeneca submitted a supplemental NDA for approval of the new formulation of DIPRIVAN with disodium edetate. After an expedited review, the FDA approved this application on June 11, 1996, permitting the sale of the reformulated product.[3/] On Dec. 10, 1998, in response to a Citizen Petition filed by Zeneca, FDA withdrew the original formulation of DIPRIVAN, which contained no antimicrobial additive, on safety grounds, under Section 505(e) of the Act, 21 U.S.C. § 355(e). See 63 Fed. Reg. 68289 (Dee, 10, 1998). Since the withdrawal and

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3/ The FDA also ultimately awarded three years of exclusivity to the revised formulation of DIPRIVAN based on the clinical studies Zeneca performed to address the safety questions created by the addition to the product of disodium edetate.

replacement of the original formulation with the new formulation of DIPRIVAN containing disodium edetate, the clusters of fever and infection associated with extrinsic contamination of the product due to misuse of the product appear to have been eliminated. Zeneca's development efforts therefore have succeeded in addressing the safety concerns associated with misuse of the original formulation of DIPRIVAN.

B. Safety, Efficacy and Antimicrobial Effectiveness Concerns with FDA Approval of Reformulations of Propofol Injectable Emulsion Without Any Antimicrobial Additive

1. The Agency May Not Approve an ANDA for A Propofol Formulation that Does Not Contain Any Antimicrobial Additive Because Portions of the NDA For DIPRIVAN® Have Been Withdrawn by FDA For Safety Reasons

Based on correspondence from Gensia Sicor Pharmaceuticals received pursuant to the Drug Price Competition and Patent Term Restoration ("Hatch-Waxman") Act,[4/] Zeneca understands that Gensia Sicor has submitted an Abbreviated New Drug Application ("ANDA"), No. 75-433, for a propofol injectable emulsion product with no antimicrobial additive but apparently relying instead on a prefilled syringe delivery system. Under the FFDCA and implementing regulations, however, FDA may not approve such an ANDA since there is no reference listed drug for such an ANDA,

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4/ Letter from Armand J. LeBlanc, Vice President, Scientific Affairs, Gensia Sicor Pharmaceuticals (Feb. 19, 1999).

Section 505 Q)(3)(I) of the Act and21 C.F.R. $314.150 specifically prohibit the Agency from approving an ANDA that relies on an NDA or ANDA that has been withdrawn or suspended for safety or effectiveness reasons.[5/] 21 U.S.C. § 355 (j)(3)(I). See also 21 C.F.R. $314.127 (a)(1 1) (stating that FDA will refuse to approve an ANDA if "FDA has determined that the reference listed drug has been withdrawn from sale for safety or effectiveness reasons . . . ." The Agency has withdrawn approval, under Section 505(e) of the Act, of those portions of the NDA held by Zeneca for DIPRIVAN that provided for a formulation which does not contain the antimicrobial additive disodium edetate due to safety problems associated with mishandling of the formulation by health care professionals. See 63 Fed. Reg. 68289 (Dec. 10, 1998). As a result, that product is no longer available as a listed drug for which an ANDA maybe referenced by Gensia Sicor or any other applicant or, consequently, approved by FDA. To conclude otherwise would directly conflict with the Agency's final action in withdrawing the original formulation of DIPRIVAN with no antimicrobial additive on safety grounds.

5/ Moreover, based on these public health concerns, we understand that FDA informed all ANDA applicants that the Agency would not approve an ANDA for a duplicate of the original DIPRIVAN® formulation. As such, Gensia Sicor may not rely on those portions of Zeneca's NDA that provide for a formulation of propofol without an antimicrobial additive.

2. FDA Regulations Do Not Permit Approval of an ANDA For a Parenteral Product that Alters or Deletes the Type of Inactive Ingredient Presented Here

FDA's regulations do not permit the Agency to approve an ANDA for a propofol product that relies on a DIPRIVAN with disodium edetate but that deletes disodium edetate from the product. An ANDA for a propofol injectable emulsion product that contains no antimicrobial additive, but relies instead on a prefilled syringe delivery system, is not permitted under FDA's regulations. The Agency allows alterations only under certain defined conditions:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant . . . . However, an applicant may seek approval of a [parenteral] drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant . . . provides information demonstrating that the differences do not affect the safety of the proposed drug product.[6/]

The regulation permits changes only in inactive ingredients that are preservatives, buffers or antioxidants; the FDA will not approve an ANDA for a parenteral drug product that contains changes in inactive ingredients other than for these three categories or the elimination of these three types of substances.[7/] The approved container labeling for DIPRIVAN reflects this

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6/ **21** C.F.R. § 314.94(a)(9)(iii).

7/ **21** C.F.R. § 314.127 (a)(n)(B) ("FDA. . . will refuse to approve [an] abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug").

distinction, stating that the product does not contain a preservative.[8/] Similarly, disodium edetate in DIPRIVAN is neither an antioxidant or buffer. As such, ANDA applicants may not obtain approval for generic versions of DIPRIVAN with disodium edetate that do not contain any antimicrobial additive because the regulations do not permit such approval for changes in parenteral products that are not alterations in preservatives, buffer, or antioxidants.

Even if the Agency deems disodium edetate to be a preservative, FDA may not approve an ANDA for a propofol product which does not contain any preservative. Although the regulations permit the Agency to approve limited substitutions of one inactive ingredient for another proposed by an ANDA, they do not permit the elimination of an inactive ingredient present in the referenced formulation. In the preamble to its regulations, FDA stated that the "applicant would be required to identify and characterize any differences between the formulation of its proposed drug product and that of the reference listed drug and include in the ANDA information to show that the inactive ingredient will not adversely affect the drug product's safety."[9/] The preamble thus contemplates that the applicant will supply information on the presence of a substitute for an

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8/ See Zeneca Pharmaceuticals, DIPRIVAN (propofol) Injectable Emulsion, Professional Information Brochure, Jan. 1998 (stating that "DIPRIVAN Injectable Emulsion can still support the growth of microorganisms as it is not an antimicrobially preserved product under USP standards").

9/ 54 Fed. Reg. 28872,28884 (July 10, 1989) (emphasis added).

inactive ingredient, but not the elimination of any such ingredient. Even if FDA believes that disodium edetate is a preservative, deletion of it from the formulation would be a significant change. It is not within the scope of the Agency's regulations for the Agency to permit the deletion of a "preservative" from the formulation, since the regulations prohibit any change to other categories of inactive ingredients for safety reasons.

Finally, if disodium edetate both is considered a preservative and the regulations permitted the deletion of a preservative altogether, Gensia Sicor's ANDA for a propofol product that has no antimicrobial additive but relies instead on a prefilled syringe cannot be approved because such a product raises serious safety concerns. FDA's regulations place strict limits on the formulation of generic parenteral drugs, creating the presumption that such drugs will be exactly the same in formulation as the reference listed drug, or if not, require the ANDA applicant to establish the safety of any change. There is no doubt that the elimination of disodium edetate from a propofol injectable emulsion product would affect the safety of the propofol product, because such a product would be a duplicate of the original formulation of DIPRIVAN which was withdrawn for safety reasons by the FDA. FDA thus cannot, consistent with its regulations, approve Gensia Sicor's ANDA for a propofol product that contains no antimicrobial additive whatsoever.

10/ 21 C.F.R. $314.9 (a)(9)(iii).

The Agency must, therefore require Gensia Sicor to submit information from studies adequate to demonstrate that the safety of its proposed formulation which does not contain any antimicrobial additive is as safe as DIPRIVAN with disodium edetate.[11/] Because clinical studies other than bioavailability or bioequivalence studies are required, an NDA rather than an ANDA will be necessary.[12/]

3. FDA May Not Approve An ANDA for a Propofol Formulation that Does Not Contain an Antimicrobial Additive Based on an NDA for a Propofol Formulation that Contains an Antimicrobial Additive

Because the original formulation of DIPRIVAN was withdrawn by FDA for safety reasons in response to Zeneca's Citizen Petition, there simply is no extant NDA that can serve as a reference-listed drug for Gensia Sicor's ANDA. FDA cannot, consistent with the Act and its regulations, approve an ANDA that references the current formulation of DIPRIVAN in support of a proposed product from which disodium edetate has been removed, and which contains no antimicrobial additive whatsoever. In view of the serious safety concerns presented by such a deletion from the only extant reference-listed drug, DIPRIVAN with an antimicrobial additive, FDA must, at a minimum, require Gensia Sicor to submit a Citizen Petition requesting permission to submit an ANDA for this type of change, because the product for which Gensia

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11/ 21 C.F.R. § 314.94(a)(9)(iii).

12/ 21 C.F.R. § 314.54(a).

Sicor is seeking approval is simply a duplicate a product which was withdrawn by the FDA for reasons of safety pursuant to Section 505(e) of the Act.

In such a Citizen Petition, Gensia Sicor must present appropriate data to FDA demonstrating that the elimination of a substance from the listed reference drug, DIPRIVAN, which is included in that drug specifically for its antimicrobial effect, is permissible and would not compromise safety. The necessity of filing of, and public comment on, a Citizen Petition by Gensia Sicor is particularly acute where the Agency has found, in final Agency action in response to Zeneca's Citizen Petition, that propofol formulations that do not contain an antimicrobial additive present safety issues due to the mishandling by health care professionals in the U. S.. The history of the original formulation demonstrates that attempts to address these safety issues due to such mishandling through educational efforts will not prevent health care professionals from mishandling the product and thus will not address the safety issues associated with misuse of the product. Only through submission of such a Citizen Petition, and public comment on the proposal, can FDA ensure that deletion of an antimicrobial additive, which additive was included at the Agency's request, from the reference listed drug can reasonably be concluded not to compromise safety because those contamination concerns can be addressed effectively solely by an alternative container or delivery system.

Moreover, the regulations do not allow any changes with respect to disodium edetate, because the agent is not a preservative, buffer or antioxidant within DIPRIVAN. In this regard, the FDA must incorporate in its analysis that Gensia Sicor has conceded in at least two filings to the Agency that FDA cannot approve a generic version of the original formulation of DIPRIVAN. As part of its Citizen Petition requesting approval to export propofol injectable emulsion 1 % to Mexico, Gensia Sicor has certified that its version of the product, which does not contain disodium edetate or any other antimicrobial additive, "does not meet the conditions of approval under the Federal Food, Drug, and Cosmetic Act ."[13/] In addition, in its comments to Zeneca's Citizen Petition requesting the Agency to withdraw portions of the NDA for DIPRIVAN without disodium edetate, Gensia Sicor also conceded that "[i]f the [FDA] were to withdraw Zeneca's unpreserved propofol formulation, such an action would preclude the pursuit of a product which surmounts the mishandling issues . . ." See Letter to FDA Docket No, 98P-0221/PSA from Gensia Sicor, dated May 29, 1998. Gensia Sicor was correct in its conclusion that FDA cannot, consistent with the Act, approve an ANDA for propofol injectable emulsion without an antimicrobial additive, in view of the absence of any reference listed drug to support filing and approval. FDA cannot simply ignore its prior conclusion,

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13/ Citizen Petition from Rosalie A. Lowe, Associate Director, Regulatory Affairs, Gensia Sicor to Dockets Management Branch, Food and Drug Administration (Sept. 30, 1998).

4. Safety, Effectiveness and Antimicrobial Efficacy Data Necessary to Support Approval of an ANDA for Propofol Injectable Emulsion Containing No Antimicrobial Additive

Based on Zeneca's experience with the original formulation of DIPRIVAN® (propofol) Injectable Emulsion in the U. S., the failure to include an antimicrobial additive in a generic version of propofol injectable emulsion will have serious safety consequences in the context of misuse. First, the use of the prefilled syringe will not offset the adverse safety effect of removing disodium edetate from the current DIPRIVAN formulation because the less desirable safety profile of DIPRIVAN without disodium edetate in the context of misuse has not been found to be specific to the containers in which the drug is packaged.[14/] In fact, practical experience with the use of prefilled syringes generally, as well as with DIPRIVAN specifically, provides strong evidence that the packaging of a propofol formulation that does not contain an antimicrobial additive in prefilled syringes will not eliminate the adverse experiences associated with mishandling of the product in the U.S. For example, it is common medical practice to mix DIPRIVAN with a variety of agents before injection. Medical personnel add alfentanil,[15/]

14/ Letter from Stephen Paul Mahinka, Counsel for Zeneca Inc., to Dockets Management Branch, Food and Drug Administration 5-6 (July 2, 1998). Zeneca expressly incorporates that discussion by reference here.

15/ Peter Isert, Propofol and Alfentanil Mixture for Outpatient Surgery, 7 J. Clinical Anesthesia 357 (1995) (attached); D.A. Wallace &J. Ryckman, Fentanyl/Propofol Does Not Prolong Emergence After ESWL When Compared to Alfentanil/Propofol, 81 Anesthesiology Al 5 (1994) (attached); I.N. Taylor, et al., Pharmacodynamic Stability (continued...)

ketamine,[16] lidocaine,[17] lignocaine,[18] methohexitone,[19] morphine,[20] prilocaine,[21] thiopental,[22]

15/(...continued)
of a Mixture of Propofol and Alfentanil, 69 Brit. J. Anesthesia 168(1 992) (attached); E. Sherry, Admixture of Propofol and Alfentanil, 47 Anesthesia 477 (1992) (attached).

16/ S. Badrinath, et al., Use of Ketamine-Propofol Admixture During Monitored Anesthesia Care, 87 Anesthesiology Al O (1 997) (attached).

17/ G.A. Kirk, et al., Lidocaine Inhibits Growth of Staphylococcus Aureus in Propofol, 77 Anesthesiology A407 (1 992) (attached).

18/ M. Eriksson, et al., Effect of Lignocaine and pH on Propofol-Induced Pain, 78 Brit. J. Anesthesia 502 (1997) (attached); D.W.J. Mecklem, Propofol Injection Pain: Comparing the Addition of Lignocaine or Metoclopramide, 22 Anesthesia & Intensive Care 568 (1994) (attached); G.N. Newcombe, The Effect, on Injection Pain, of Adding Lignocaine to Propofol, 18 Anesthesia& Intensive Care 105 (1990) (attached).

19/ N. Thompson& G.S. Robertson, Comparison of Propofol and a Propofol and a Propofol-Methohexitone Mixture for Induction of Day-Case Anesthesia, 77 Brit. J. Anesthesia 213 (1997) (attached).

20/ S.E. Bree, et al., Combining Propofol with Morphine in Patient-Controlled Analgesia to Prevent Postoperative Nausea and Vomiting, 80 Brit. J. Anesthesia 152 (1998) (attached).

21/ M. Eriksson, Prilocaine Reduces Injection Pain Caused by Propofol, 39 Acta Anaesthesiologica Scandinavia 210 (1995) (attached).

22/ Edward R. Lazar, et al., Propofol and Thiopental in a 1:1 Volume Mixture Is Chemically Stable, 86 Anesthesia& Analgesia 422 (1998) (attached); D.T. King, et al., HPLC Determination of Propofol-Thiopental Sodium and Propofol-Ondansetron Mixtures, 19 J. Liquid Chromatography & Related Tech., 2285 (1996) (attached); Richard J. Prankerd & R. Douglas Jones, Physiochemical Compatibility of Propofol with Thiopental Sodium, 53 Am. J. Health-System Pharmacy 2606 (1996) (attached); Eric L. Chernin, et al., Stability of Thiopental Sodium and Propofol in Polypropylene Syringes at 23 and 4°C, 53 Am. J. Health-System Pharmacy 1576 (1996) (attached);
(continued...)

thiopentone,[23] diluents[24], and combinations of substances[25] to DIPRIVAN before injecting it. It is likely that such mixing would continue to occur, even with propofol injectable emulsion packaged in prefilled syringes -- either in the packaging syringe, or in a separate syringe or container. This mixing process can introduce pathogens into the mixture either directly by standard "touch" contamination,[26] or indirectly through addition of drugs from multiple use

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22/(...continued)
John Crowther, et al., Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture of Propofol and Thiopental, 82 Anesthesia& Analgesia 475 (1996) (attached).

23/ Saifudin Rashiq, et al., Recovery Characteristics Following Induction of Anesthesia with a Combination of Thiopentone and Propofol, 41 Can. J. Anaesthesia 1166 (1994); M. Naguib &A. Sari-Kouzel, Thiopentone-Propofol Hypnotic Synergism in Patients, 67 Brit. J. Anesthesia 4 (1991) (attached).

24/ Jens Rau, et al., Reducing Pain During Propofol Injection: Role of the Solvent, 76 Brit. J. Anesthesia S2 (1996) (attached) (saline and Intralipid); Valérie Saitou-Miranda, et al., Compatibility of Propofol Diluted in 5% Glucose with Glass and Plastics (Polypropylene, Polyvinylchloride) Containers, 130 Int'l J. Pharmaceutics 130 (1996) (attached) (glucose); W. Klement & J.O. Arndt, Pain on Injection of Propofol: Effects of Concentration and Diluent, 67 Brit. J. Anaesthesi~281 (1991) (attached) (glucose and Intralipid).

25/ Peter R. Isert, et al., Compatibility of Propofol, Fentanyl, and Vecuronium Mixtures Designed for Potential Use in Anesthesia and Patient Transport, 8 J. Clinical Anesthesia 329 (1996) (attached); P.R. Isert, et al., In Vitro Compatibility Testing of Two Intravenous Anesthesia Admixtures, 23 Anaesthesia & Intensive Care 644(1995) (attached) (fentanyl and vecuronium); P.R. Isert & M. Beaudoin, Clinical Evaluation of Intravenous Anesthetic Admixture, 23 Anesthesia& Intensive Care 644 (1995) (attached) (fentanyl and vecuronium); R. Baile, et al., Total Intravenous Anesthesia for Laparoscopy, 44 Anesthesia60(1989) (attached) (alfentanil and vecuronium).

26/ Way Y. Huey, et al., Microbial Contamination Potential of Sterile Disposable Plastic (continued...)

containers that have themselves been contaminated.[27] As a result, despite the packaging of the product in prefilled syringes, patients administered these mixtures may suffer adverse health effects, particularly where there is any delay between the mixing and administration of the product. Notably, it is in just this situation that the inclusion of disodium edetate in the propofol injectable emulsion is likely to reduce the risk to patients of any adverse health effects from the inadvertent introduction into the mixture of any pathogen. Consequently, a formulation of propofol injectable emulsion that contains no antimicrobial additive that is administered in a prefilled syringe must be proven to provide at least the same level of antimicrobial efficacy as DIPRIVAN with disodium edetate.

In addition, the stopcocks or rubber injection ports through which propofol injectable emulsion may be added to I.V. lines also can be a source of contamination.[28] Moreover, trace amounts of

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26/(...continued)
Syringes, 42 Am. J. Hospital Pharmacy 102 (1985) (attached).

27/ Arnold J. Berry, Practical Issues in Outpatient Anesthesia -- Practical Infection Control, 42 Can. J. Anesthesia 1051 (1995) (attached); Anita K. Highsmith, et al., Growth of Nosocomial Pathogens in Multiple-Dose Parenteral Medication Vials, 15 J. Clinical Microbiology 1024 (1982).

28/ See M. Trautmam, et al., Bacterial Colonization and Endotoxin Contamination of Intravenous Infusion Fluids, 37 J. Hosp. Infection 225 (1997) (attached); Yoshifumi Inoue, et al., Prevention of Catheter-Related Sepsis During Parenteral Nutrition: Effect of a New Connection Device, 16 J. Parenteral & Enteral Nutrition 581 (1992) (attached); Sue Crow, et al., Microbial Contamination of Arterial Infusions Used for
(continued...)

propofol injectable emulsion that remain inside I.V. lines can support the multiplication of pathogens that are introduced through later, unrelated handling of the I.V. lines, and similarly small amounts of blood found in lines can contaminate a syringe that is used to inject product into a different patient's I.V. line.[29/] Back flow of blood from a patient's own vascular system can occur depending upon the pump pressure used for infusion, the height of the pump relative to the patient's heart, and the patient's own blood pressure, resulting in introduction of blood into the line. Failure to change I.V. lines in accordance with the product labeling can also result in contamination. All of these types of contamination are equally likely regardless of the use of a prefilled syringe or a syringe that is filled from a vial or an ampule. Notably, health care workers have been reported to be misusing DIPRIVAN in a number of ways that can contribute to the routes of contamination described above, including reusing the same syringes and/or infusion

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28/(...continued)
Hemodynamic Monitoring: A Randomized Trial of Contamination with Sampling Through Conventional Stopcocks Versus a Novel Closed System, 10 Infection Control & Hosp. Epidemiology 557 (1989) (attached); J.L. Parlow, Blood Contamination of Drug Syringes Used in Anesthesia, 36 Can. J. Anesthesia S61 (1989) (attached),

29/ Michael R. Cohen, Reuse of Syringes for Multiple Patients? It May Be Happening in Your Hospital!, 31 Hosp. Pharmacy 84 (1996) (attached); Donald R. Miller, Anesthesia Drug Costs and Utilization -- Time for a Critical Re-appraisal, 43 Can. J. Anesthesia 4(1 996) (attached); Gareth S.A. Kantor & Frances Chung, Anesthesia Drug Cost, Control and Utilization in Canada, 43 Can. J. Anaesthesia 9 (1996) (attached); Elizabeth J. Monti, The Safe Use of Disposable Syringes in Anesthesia: Cost Effective or Costly?, 6 CRNA: Clinical Forum Nurse Anesthetists 86 (1995) (attached).

pump lines on different patients and transferring filled syringes between operating rooms or facilities.[30/] Consequently, adverse experiences associated in the U.S. with mishandling of propofol injectable emulsion without disodium edetate would be almost certain to occur despite the packaging of the product in prefilled syringes.

Gensia Sicor has previously acknowledged this irreducible risk in filings to FDA. In an ANDA Suitability Petition, Gensia Sicor claimed that the short time period over which a 20 mL syringe is likely to be used would "mitigat[e] the time period for microbial growth."[31/] Clearly, no such mitigation would be necessary if a prefilled syringe prevented the introduction of pathogens into propofol injectable emulsion. Moreover, a determination that propofol injectable emulsion packaged in a 20 mL prefilled syringe would be used too quickly to permit the multiplication of

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30/ S.A.R. Webb, @ al., Contamination of Propofol Infusions in the Intensive Care Unit: Incidence and Clinical Significance, 26 Anesthesia& Intensive Care 162 (1998) (attached); Shri N. Bennet, et al., Postoperative Infections Traced to Contamination of an Intravenous Anesthetic, Propofol, 333 N. Eng. J. Med. 147 (1995) (previously supplied); A. Bach & J. Motsch, Infectious Risks Associated with the Use of Propofol, Acts Anaesthesiologica Scandinavia 1189 (1996) (attached). See also Ronald L. Nichols & Jeffrey W. Smith, Bacterial Contamination of an Anesthetic Agent, 333 N. Eng. J. Med. 184 (1995) (previously supplied) (describing similar lapses).

31/ ANDA Suitability Petition from Rosalie A. Lowe, Associate Director, Regulatory Affairs, Gensia Sicor Pharmaceuticals, to Dockets Management Branch, Food And Drug Administration 4 (Feb. 6, 1998) (Docket No. 98P-0069, filed Feb. 9, 1998), withdrawn by Letter from Rosalie A. Lowe, Associate Director, Regulatory Affairs, Gensia Sicor Pharmaceuticals, to Dockets Management Branch, Food And Drug Administration (Feb. 20, 1998).

pathogens assumes complete compliance with product labeling.[32/] However, theproposed use of prefilled syringes to cure a problem that results directly from noncompliance with product labeling -- the failure to observe proper aseptic technique and the use of containers of product for multiple patients -- is faulty. It is illogical to assume hypothetically that health care professionals will comply with product labeling in one circumstance -- the use of prefilled syringes -- while knowing from experience that health care professionals do not follow the same product labeling in another circumstance -- the use of other packaged forms of the product.

FDA must also consider that at least one additional practice potentially resulting in extraneous infection -- the pooling of the contents of several 20 mL syringes for large-volume infusion applications -- may occur. It can reasonably be expected that medical professionals will remove and combine the contents of several 20 mL syringes to use in these larger volume applications, resulting in increased product manipulation, with a consequent risk of infection. This is a significant risk as a practical matter because prefilled 20 mL syringes cannot be used in the volumetric infusion pumps which are prevalent in U.S. ICUs. The temptation and opportunity to combine the contents of prefilled syringes for use in these devices is likely to be substantial. Any such uses would result in increased handling of the product and an increased risk of

32/ Id. at **4.**

inadvertent contamination. The history of DIPRIVAN has demonstrated that mishandling of the product in the U.S. could not be eliminated.

Before Gensia Sicor's proposed product maybe approved, therefore, it must demonstrate through scientific data and clinical studies that the absence of any antimicrobial additive from a propofol injectable emulsion does not adversely affect safety.[33/]

5. The Agency May Not Approve an ANDA for a Propofol Formulation that Does Not Contain Any Antimicrobial Additive Unless the Applicant Submits In Vivo Studies Demonstrating that the Formulation Is Bioequivalent to the Reference Listed Drug

Section 505(j) (2)(A)(iv) of the Act and 21 C.F.R. $314.93 require an ANDA applicant to include information in the application showing that the generic drug product is bioequivalent to the reference listed drug product upon which the applicant relies or, where the generic drug product is not identical to the listed drug in route or administration, dosage form, and strength, to submit a suitability petition requesting permission to make such change. Accordingly, Gensia Sicor must show that the rate and extent of absorption of its proposed generic drug does not differ significantly from the rate and extent of absorption of the pioneer drug. 21 U.S.C. §

33/ Gensia Sicor must demonstrate that the elimination of the antimicrobial additive from propofol will not affect safety, 21 C.F.R. $314.94 (a)(9)(iii).

355(j)(7)(A); 21 C.F.R. 320.1(e). Such information normally must be supported by in vivo studies demonstrating that the generic drug product is bioequivalent to the reference listed drug. 21 C.F.R. $320.21. These requirements are intended to ensure that the generic drug product is as safe and effective as the reference listed drug product.

Under certain limited circumstances the Agency may waive this requirement. FDA, for example, may waive the requirement of in vivo studies for an ANDA where the proposed product is a "parenteral solution intended solely for administration for injection . . . and contains the same active and inactive ingredients." 21 C.F.R. $320.22. (b)(1) (emphasis added). Such a waiver, however, does not apply to products such as that proposed by Gensia Sicor which are to parenteral emulsions, and which do not contain all of the same inactive ingredients as the reference listed drug.

Consistent with the Act and the Agency's regulations, therefore, FDA may not waive its mandate to protect the public health in this situation and must require Gensia Sicor or any other applicant to submit in vivo studies demonstrating that a propofol injectable emulsion, which is packaged in a prefilled syringe or other delivery system and contains no antimicrobial additive, nonetheless is bioequivalent to DIPRIVAN with disodium edetate.

6. The Restrictions on Labeling Differences in FDA's Regulations Prohibit the Agency from Approving an ANDA for Propofol that is Packaged in a Prefilled Syringe and Does Not Include Within its Labeling All of the Approved Indications and Usages for DIPRIVAN

Pursuant to the FFDCA and the Agency's regulations, FDA may not approve an ANDA that fails to show that the proposed labeling for the generic drug is the same as that of the reference listed drug or qualifies for an exception to labeling requirements under the Act. 21 U.S.C.§ 355 (j)(2)(a)(i).[34/] This prohibition is based on the premise that significant variance from the label of a drug product that has been proven to be safe and effective negates the presumption that the generic drug product is bioequivalent to the reference-listed drug product and, thus, is safe and effective. Indeed, FDA has stated that "[consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand name counterpart," and FDA in several instances has, therefore, denied approvals to generic drug manufacturers for drugs where the product label manifests significant variations between the

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34/ See also H.R. No. 98-857, Part I at 21,26 (1984), reprinted in 1984 U. S. C. C.A.N. 2647, 2658. ("[A]n ANDA must be disapproved if it fails to show that the proposed labeling for the generic drug is that same as that of the listed drug. Changes in the proposed labeling due to the fact that the generic drug is produced or distributed by a different manufacturer are not a ground for disapproval. Similarly, changes in the proposed labeling of the generic drug because a petition regarding a change has been granted is not grounds for disapproval.")

label for a generic drug product and the label for the pioneer drug product. See. e.g., 57 Fed. Reg. 17960, 17961 (April 28, 1992).

While FDA regulations permit some differences in the labels of a generic and its corresponding pioneer drug, these exceptions are very narrow. The FFDCA permits the label for a generic drug to differ from that of the pioneer drug only to accommodate certain permissible compositional differences between the generic and pioneer drugs. 21 U.S.C. § 355(j)(2)(a)(v), (2)(C); see also 21 C.F.R. $314.94. Variations between the label for the generic drug product and the pioneer drug product are also permitted to reflect: (1) differences in the expiration date, formulation, bioavailability, or pharmacokinetics of each drug; (2) labeling revisions in accordance with current FDA guidelines or guidances; or (3) the omission of an indication or other aspect of labeling protected by patentor accorded exclusivity under the Act. See 21 C.F.R.§ 3 14.94(a)(8); see also 57 Fed. Reg. 17959, 17961 (April 2, 1998) (stating that "except for labeling differences due to exclusivity or a patent and differences under section 355(j)(2)(v) of the Act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for the ANDA approval"); 54 Fed. Reg. 28872,28884. If a prefilled syringe of propofol without any antimicrobial additive is approved, the differences in the labeling that likely must be included would not be the type of labeling differences permitted under the

Agency's regulations and, consequently, the FDA cannot approve Gensia Sicor's ANDA, unless the labeling for its prefilled syringe product is the same as that for DIPRIVAN.

Gensia Sicor has conceded that it believes that its single use 20 mL pre-filled syringe would not "represent the configuration of choice for use in MAC or ICU sedation" because the "smaller volume of 20 mL would not be considered convenient for use in MAC or ICU sedation, since the use of a 20 mL dosage form would require frequent replacement of the product as compared to Zeneca's larger volume configurations of 50 mL and 100 mL." See Gensia Sicor Suitability Petition, dated February 6, 1998, 98 P-0069. Any labeling that is approved by FDA for a formulation of propofol that is packaged in a 20 mL syringe thus would likely not be identical to the labeling for the reference listed product, DIPRIVAN with disodium edetate. As Gensia Sicor has conceded, the labeling likely would not include indications for MAC and ICU sedation, indications that are included in Zeneca's labeling for DIPRIVAN with disodium edetate. Any labeling for a propofol product packaged in a 20 mL syringe thus likely would differ substantially from the label for the reference-listed product. Such differences are not within any of the limited exceptions to the requirement that the label for a generic product and the reference listed drug product be the same. Consequently, FDA cannot approve the ANDA filed by Gensia Sicor.

7. The Agency May Not Approve An ANDA for a Propofol Formulation Because FDA Has Granted Zeneca DIPRIVAN Three Years of Market Exclusivity

Zeneca has been granted exclusivity for the new formulation of DIPRIVAN effective until June 11, 1999. The formulation of DIPRIVAN is the only reference listed drug to which all ANDA applicants must refer. Consequently, the Agency may not approve an ANDA for any propofol formulation packaged in a prefilled syringe or any other delivery system until the exclusivity period granted to DIPRIVAN has expired. Accordingly, no propofol injectable emulsion product can be approved unless an applicant conducts the necessary preclinical, clinical, and other scientific investigations to confirm the safety and efficacy of the product.

Iv. Zeneca Will Suffer Irreparable Injury if the Stay is not Granted

The failure of the FDA to grant the stay requested in this Petition will result in irreparable injury to Zeneca. Zeneca's reputation and the good will it has developed for DIPRIVAN® (propofol) Injectable Emulsion will be damaged by the improper attribution to DIPRIVAN with disodium edetate of adverse effects deriving from the mishandling of generic forms of propofol injectable emulsion without any antimicrobial additive. Zeneca has marketed DIPRIVAN products in the U.S. for over nine years. During this time, DIPRIVAN has been recognized as a safe and effective drug when handled and administered appropriately under aseptic conditions in

accordance with the approved instructions, and has been used in countless surgical procedures and in ICUS throughout the U. S..

If the FDA denies this Petition for stay, a generic form of propofol injectable emulsion will be introduced into the market with no antimicrobial additive. There is no doubt that some medical professionals in the U.S. will mishandle this product and a number of patients will experience adverse effects as a result. Therefore, Zeneca's reputation, and the good will associated with DIPRIVAN, will be irreparably injured, despite Zeneca's significant efforts to provide a product that can perform safely even under conditions of misuse.

v. **Zeneca's Case Is Not Frivolous and Is Being Pursued in Good Faith**

Shortly after the discovery of adverse experiences associated with mishandling of the original formulation of DIPRIVAN® (propofol) Injectable Emulsion, Zeneca undertook significant research and clinical testing to identify an appropriate antimicrobial additive to retard microbial growth in propofol injectable emulsion. Through this process, Zeneca developed considerable expertise and experience regarding the inclusion of antimicrobial additives in propofol injectable emulsion and the adverse experiences that can occur from mishandling of the propofol formulations that do not include any antimicrobial additive. Approval by FDA of Gensia Sicor's

or any other applicant's ANDA for a product not containing any antimicrobial additive thus raises significant safety issues which support grant of this Petition for Stay.

VI. There Are Sound Public Policy Grounds Supporting the Stay

There are sound public policy grounds for the FDA to grant the stay that Zeneca requests in this Petition. The initial formulation of DIPRIVAN® (propofol) Injectable Emulsion was a unique therapeutic product, the benefits of which outweighed the risks resulting from mishandling. However, the original product, without an antimicrobial additive, presents a comparatively much less desirable safety profile in the context of mishandling than the new product with disodium edetate, with no concomitant increase in therapeutic benefit. The Agency confirmed this conclusion in its final action withdrawing on safety grounds the original formulation of DIPRIVAN in response to Zeneca's Citizen Petition. Public policy also supports grant of this stay petition because for the Agency to do otherwise would result in an unlawful, arbitrary and capricious decision by the Agency in view of its withdrawal of the original formulation of DIPRIVAN on safety grounds.

VII. The Delay Resulting from the Stay Is Not Outweighed by Public Health or Other Public Interests

The formulation of DIPRIVAN® (propofol) Injectable Emulsion containing disodium edetate is at least as safe and effective as any proposed generic versions of propofol injectable emulsion containing no antimicrobial additive whatsoever. As such, any delay of approval of Gensia Sicor's ANDA will not deprive U.S. consumers of a needed anesthetic product and will not conflict with the public health interest in the availability of useful medical products.

The granting of a stay will instead forward an important public interest by assuring the proper application of the Agency's regulations that are intended to protect U.S. consumers from unsafe products. Any delay resulting from the stay will permit and require Gensia Sicor to demonstrate to the FDA that:

1. The elimination of disodium edetate, and the absence of any antimicrobial additive whatsoever is permitted by FDA's regulations, and does not affect the safety or therapeutic efficacy of the formulation in the clinical setting in which the product is intended to be used, in accordance with approved labeling;

2. The design, construction, operation, and likely use by healthcare professionals of the prefilled syringe without any antimicrobial additive will inhibit microbial growth to at least the same extent as does disodium edetate in the current formulation of DIPRIVAN;

4. In vivo studies show that the generic product is bioequivalent to DIPRIVAN with disodium edetate; and

5. The new design, construction and operation of the syringe does not affect the physiochemical properties of the formulation, e.g., stability.

6. The propofol product packaged in a prefilled syringe does not infringe on the three years of market exclusivity granted to Zeneca's DIPRIVAN.

Accordingly, the delay in approval of the new product resulting from the stay will serve, rather than contravene, important public interests by ensuring that elimination of disodium edetate from Gensia Sicor's prefilled syringe version nonetheless leaves the generic product with a safety and therapeutic and antimicrobial efficacy profile at least equal to that of DIPRIVAN with disodium edetate.

VIII. Conclusion

Zeneca respectfully requests that, for the above described reasons, and as mandated by the FFDCA and the FDA's implementing regulations, the FDA promptly stay any pending, tentative, or final approval of an ANDA by Gensia Sicor or any other applicant for a generic version of DIPRIVAN® (propofol) Injectable Emulsion which does not contain any antimicrobial additive, pending the expiration of the three years of market exclusivity granted to DIPRIVAN and the completion of adequate clinical and other scientific studies to demonstrate the safety of such a product

Respectfully submitted,

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Attachments